REMARKS

I. Current status

Claims 4-6 and 19-20 are pending in this application. Claim 4 has been amended. Claims 19 and 20 have been added. Support for the amendments and added claims can be found throughout the specification and original claims. For example, support can be found on page 16, lines 5-24. No new matter has been added.

II. Rejections under 35 U.S.C. § 112, second paragraph

Claims 4-6 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for reciting "including" and having an improper Markush recitation. Applicants traverse the rejection because the claims are clear and definite as written. In order to even more clearly recite the claimed subject matter, however, claim 4 has been amended to exclude the term "including" and also to include appropriate Markush language. Accordingly, Applicant respectfully requests reconsideration and withdrawal of the rejection of the claims.

III. Rejections under 35 U.S.C. § 112, first paragraph

Claim 5 stands rejected under 35 U.S.C. § 112, first paragraph, as allegedly being non-enabled by the specification. Applicant traverses the rejection because the claim is well enabled.

Applicants thank the Examiner for indicating that the claim is enabled for the disorders of stroke, anxiety and depression.

As will be recognized, the enablement requirement of §112 is satisfied so long as a disclosure contains sufficient information that persons of ordinary skill in the art having the disclosure before them would be able to make and use the invention. *In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988)(the legal standard for enablement under §112 is whether one skilled in the art would be able to practice the invention without undue experimentation).

Applicant asserts that treatment of disorders characterized by hypersecretion of CRF is well-enabled by the specification because undue experimentation would not be required to carry out such treatment. It was well known in the art, at the time the application was filed, that hypersecretion of CRF was linked to numerous disorders. It was also well known in the art at

the time the application was filed, that CRF antagonists could ameliorate and even prevent the symptoms associated with elevated levels of CRF in animal models for various known disorders. Thus, it was well recognized that CRF antagonists could have broad activity for treating a wide array of disorders. Some specific references pertaining to the successful testing of CRF antagonists in animal models are provided below.

McCarthy, *et al.*, *Current Pharmaceutical Design*, **1999**, *5*, 289, enclosed herewith, is a review article summarizing much of the research published describing the use of CRF antagonists for the treatment of numerous disorders. While the publication date of this article is after the filing date of the present application, as a review article, it cites numerous works that were published prior to or around the filing date of the present application. For example, Table 9 summarizes cumulative evidence for the effectiveness of CRF antagonists in animal models of CRF-related disorders such as depression, anxiety, substance abuse, seizures, inflammation, and pre-term labor.

Burks *et al.*, U.S. Pat. No. 5,236,901 (1993), enclosed herewith, reports the effectiveness of a CRF antagonist in animal models for functional bowel disease, such as irritable bowel syndrome (see, e.g., Example 5).

Maecker, *et al.*, *Brain Research*, **1997**, *744*, 166, herewith enclosed, reports a CRF antagonist having neuroprotective activity in relation to seizures.

Chalmers, *et al.*, *TiPS*, **1996**, *17*, 166, herewith enclosed, provides a review of the literature, reporting that hypersecretion of CRF is associated with not only anxiety and depression (for which the methods of the present invention have been deemed enabled), but with eating disorders such as anorexia nervosa, stroke, and inflammatory disorders. The authors also propose that CRF antagonists may be effective treatments for such disorders (see, e.g., Figure 4, pg. 172).

In view of the overwhelming evidence provided above that CRF antagonists are useful for treating a wide range of disorders, all of which are characterized by hypersecretion of CRF, there would be no undue experimentation required to practice the invention. If experimentation were necessary, such as for correlating CRF levels with disease states, testing compounds for CRF antagonist activity, or testing compounds for efficacy in animal models, such experimentation would be routine in the art. As has been well-established in the courts, "the test

[for undue experimentation] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine... *In re Wands*, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988) (citing *In re Angstadt*, 537 F.2d 489, 502-04, 190 U.S.P.Q. 214, 217-19 (C.C.P.A. 1976)).

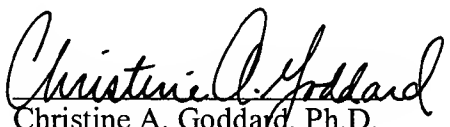
The Office Action attempts to support the non-enablement rejection by citing Mitchell, *Neurosci. Biobehav. Rev.* **1998**, *22*, 635, incorrectly asserting that this reference shows that one cannot rely on hypersecretion of CRF to predict treatable disorders because the true causes of disorders associated with elevated CRF levels, such as anxiety and depression, are unknown. This reasoning fails to show non-enablement of the claim, because the cause of elevated CRF levels is not relevant to the claimed subject matter. The claim is concerned with hypersecretion of CRF, not why or how hypersecretion came about.

In view of the above evidence, showing that numerous disorders are associated with hypersecretion of CRF, and many are treatable in animal models by administration of a CRF antagonist, the claims are well enabled. Accordingly, Applicant respectfully requests reconsideration and withdrawal of the rejection of the claims.

In view of the foregoing, Applicant submits that the claims as amended are in condition for allowance, and an early Office Action to that effect is earnestly solicited.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned **"Version with markings to show changes made."**

Respectfully submitted,



Christine A. Goddard, Ph.D.
Registration No. 46,731

Date: 10-9-02

Bristol-Myers Squibb Company
Experimental Station
Bldg. E353, Suite 133B
Route 141 and Henry Clay Road
Wilmington, DE 19880

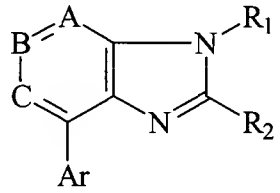
(302) 467-5263 (phone)
(302) 467-6701 (fax)

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claim 4 has been amended as follows:

4. (amended once) A compound having the following structure:



[including stereoisomers and pharmaceutically acceptable salts] stereoisomer or pharmaceutically acceptable salt form thereof, wherein:

A, B and C are selected from CR and N, with the proviso that when B is N both A and C are CR;

R is selected from hydrogen and C_{1-6}alkyl;

R_1 is selected from NR_3R_4 and R_5;

R_2 is C_{1-6}alkyl;

R_3 is selected from hydrogen, C_{1-6}alkyl, mono- or di(C_{3-6}cycloalkyl)methyl, C_{3-6}cycloalkyl; C_{3-6}alkenyl; hydroxyC_{1-6}alkyl, C_{1-6}alkylcarbonyloxyC_{1-6}alkyl and C_{1-6}alkyloxyC_{1-6}alkyl;

R_4 and R_5 are independently selected from C_{1-8}alkyl, mono- or di(C_{3-6}cycloalkyl)methyl, Ar^1CH_2, C_{3-6}alkenyl, C_{1-6}alkyloxyC_{1-6}alkyl, hydroxyC_{1-6}alkyl, thienylmethyl, furanylmethyl, C_{1-6}alkylthioC_{1-6}alkyl, morpholinyl, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, di(C_{1-6}alkyl)amino, C_{1-6}alkylcarbonylC_{1-6}alkyl, C_{1-6}alkyl substituted with imidazolyl; or a radical of the formula -(C_{1-6}alkanediyl)-O-CO-Ar^1;

or R_3 and R_4 taken together with the nitrogen atom to which they are attached form a pyrrolidinyl, piperidinyl, homopiperidinyl or morpholinyl group, optionally substituted with C_{1-6}alkyl or C_{1-6}alkyloxy;

Ar is selected from phenyl substituted with 1, 2 or 3 substituents independently selected from halo, C_{1-6}alkyl, [triflouromethyl] trifluoromethyl, cyano, C_{1-6}alkyloxy, benzyloxy,

C_{1-6}alkylthio, nitro, amino and mono- and di(C_{1-6}alkyl)amino; and pyridinyl substituted with 1, 2 or 3 substituents independently selected from halo, C_{1-6}alkyl, [triflouromethyl] trifluoromethyl, hydroxy, cyano, C_{1-6}alkyloxy, benzyloxy, C_{1-6}alkylthio, nitro, amino, mono- and di(C_{1-6}alkyl)amino and piperidinyl; and

Ar^1 is selected from phenyl, pyridinyl, and phenyl substituted with 1, 2 or 3 substituents independently selected from halo, C_{1-6}alkyl, C_{1-6}alkyloxy, di(C_{1-6}alkyl)aminoC_{1-6}alkyl, [triflouromethyl] trifluoromethyl and C_{1-6}alkyl substituted with morpholinyl.